

In re application of C. R. Maliszewski, et al.
U.S. Application No. 09/807,660

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REMARKS

Reconsideration of the allowability of the present application in view of the above amendments and the following remarks is requested respectfully.

Status of the Claims

Claims 1-6 and 19-41 were acted upon by the Examiner. Claim 7 was not acted on by the Examiner. Claim 19 has been withdrawn from consideration. Claims 1-6 and 20-41 have been rejected. Claims 4 and 6 have been cancelled. Claims 1-3, 5, 7, 20 and 21 have been amended.

Applicants' Invention

The present invention relates to a method for inhibiting platelet activation and recruitment in a mammal in need of such treatment by administering certain fusion polypeptides that contain soluble CD39 having apyrase activity. Apyrases catalyze the hydrolysis of nucleoside tri- and/or di- phosphates.

ADP is a powerful agonist of platelet activation and recruitment. Applicants have demonstrated that CD39 is an ecto-ADPase (apyrase) responsible for inhibition of platelet function. To study the effects of CD39, Applicants have generated a number of fusion polypeptides comprising soluble CD39. Applicants have tested some of these constructs for their effectiveness in inhibiting platelet activation and recruitment *in vitro*, *ex vivo*, and *in vivo*. Applicants have also correlated the apyrase activity of the fusion polypeptides with their biological activity *in vivo*.

Applicants have made the unexpected discovery that the addition of one or more amino acids added to the N-terminus of a soluble CD39 polypeptide results in improved expression levels, stability and/or activity of the CD39 polypeptide. Based on this discovery, Applicants have devised a method of using these fusion polypeptides for inhibiting platelet activation and recruitment in a mammal.

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Discussion of Examiner's Rejections and Objections

The Examiner's rejections and objections are discussed in the following order: (A) enablement and written description rejections, (B) indefiniteness rejections, (C) art rejections, and (D) claims and drawings objections.

A. **Section 112, Paragraph 1 Rejections of Claims 1-6 and 20-41**

Claims 1-6 and 20-41 were rejected by the Examiner under 35 U.S.C. § 112, first paragraph for claiming subject matter that is (1) not enabled by the specification and (2) not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants have grouped the discussion of the Examiner's enablement and written description rejections into one section because the Examiner uses the same or very similar arguments to reject the claims under these two statutory requirements. As amended, pending claims 1-3, 5, and 20-41 are adequately described and enabled by the specification.

Applicants address each of the Examiner's grounds of rejection on a claim-by-claim basis as follows.

Rejection of Claim 1 under §112, ¶1 – The Examiner asserts that the specification does not provide sufficient guidance as to the structure of (1) heterologous peptides capable of adopting a stable secondary structure, and (2) fragments and variants of SEQ ID NO: 2 such that the fragment or variant maintains its function, particularly since the term "having" in (a) is open-ended.

Claim 1 is directed to a method for inhibiting platelet activation and recruitment in a mammal in need of such treatment comprising administering an effective amount of a soluble CD39 polypeptide consisting of a structure X-Y. Claim 1 has been amended to more particularly recite the specific fusion polypeptides disclosed in applicants' specification. In particular, X is now defined as an Ala residue, amino acids 1-15 of SEQ ID NO:6, amino

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acids 25-35 of SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, or amino acids 21-24 of SEQ ID NO:30. Support for this amendment can be found in the sequence listing as filed and on page 38, lines 1-5; page 39, lines 9-12; and page 40, lines 11-19. Each of these sequences is within the scope of the elected embodiments because X is an Ala residue or a portion of "IL-2 capable of adopting a stable secondary structure" as per elected Group I. Y is now defined as (a) amino acids 36-478 of SEQ ID NO:2, (b) consecutive sequences of amino acids 36-478 of SEQ ID NO:2 with apyrase activity, (c) a variant polypeptide 95% identical in sequence to amino acids to (a) or (b), or (d) a polypeptide of (a), (b) or (c) with at least one conservative amino acid substitution. Support for this amendment can be found in the sequence listing as filed; Figure 2; and on page 9, line 35 to page 10, line 4; and page 10, lines 10-37.

With respect to subpart (b), (c), and (d) of amended claim 1, applicants have adequately described the polypeptides within the scope of these subparts by providing the amino acid sequence in the sequence listing as filed (SEQ ID NO:2). The written description requirement does not require a description of the complete structure of every species within a chemical genus. *See Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988). In *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002), the Federal Circuit made clear that the written description requirement can be satisfied in a number of ways by disclosing, for example, "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." Particularly relevant to this case, the Board of Patent Appeals and Interferences recently recognized that a claim drawn to a naturally occurring polypeptide that is at least 95% identical to a disclosed sequence is adequately described by the specification. *Ex parte Bandman*, Appeal No. 2004-2319 at p. 5 (BPAI 2005) (unpublished) (enclosed with Reply).

Here, Applicants have provided the complete structure of SEQ ID. NO:2. Applicants have also disclosed the putative domain of soluble CD39 involved in apyrase activity. See Figure 2. Thus, with respect to subpart (b) one of skill in the art would be able to identify and

verify, using the assays described in the specification, a consecutive amino acid sequence that has apyrase activity. With respect to subpart (c), applicants have provided guidance on page 10, lines 22-37 regarding how to select a polypeptide that is 95% identical to a given sequence. With respect to subpart (d), applicants have also provided on page 9, line 35 to page 10, line 4 of the specification a list of conservative amino acid substitutions. Moreover, such conservative substitutions were well-known in the art at the time this application was filed. Accordingly, applicants disclosure of the structure in SEQ ID NO:2 coupled with the identity of the apyrase domain of CD39 and the assays to test apyrase activity is more than enough to adequately describe the polypeptides to one of skill in the art within the scope of claim 1.

With respect to the enablement requirement, MPEP §2164.01 provides that the test for enablement requires a determination as to whether one of skill in the art can practice the claimed invention without *undue* experimentation. Such is the case here. In *Bandman*, the BPAI reversed the Examiner's enablement rejection of a claim drawn to a naturally occurring polypeptide that is at least 95% identical to a disclosed sequence. *Ex parte Bandman*, Appeal No. 2004-2319 at p. 7. The Examiner in *Bandman* was asserting essentially the same argument as being asserted here – that in order to satisfy the enablement requirement, the specification must provide guidance regarding the specific amino acid residues that are tolerant to change without affecting activity. *Id.*

Here, the claimed invention is a method for inhibiting platelet activation and recruitment in a mammal in need of such treatment comprising administering an effective amount of a soluble CD39 polypeptide consisting of a structure X-Y. As amended, Claim 1 provides sufficient direction as to the amino acid sequences for both the X and Y portion of the polypeptide. One skilled in the art, seeking to practice such a method can simply use the assays described in the specification to screen the polypeptides within the scope of subparts (b), (c), and (d) for apyrase activity and inhibition of platelet activity and recruitment. In particular, the Examiner is respectfully directed to Examples 7 and 15 which are directed to a phosphate release assay for ATPase activity and a platelet aggregation assay which may be

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used to determine if a given polypeptide possesses the desired biological activity.
Accordingly, as amended, Claim 1 is both described and enabled by the specification.

Rejection of Claim 2 under §112, ¶1 – The Examiner asserts that use of the term “having” is open-ended and that there is no disclosure regarding which amino acids may be added to SEQ ID NO:2. The Examiner further asserts that the specification does not provide sufficient guidance as to which amino acids may be modified such that the resulting polypeptide has the percent identity claimed and maintains its function, and that there is no disclosure as to how to measure percent identity.

Claim 2 has been amended to define Y as a polypeptide consisting of amino acids 38-476 or 39-476 of SEQ ID NO:2. Accordingly, the Examiner’s rejection is now moot and should be withdrawn.

Rejection of Claim 3 under §112, ¶1 – The Examiner asserts that the specification does not provide sufficient guidance as to the structure of the “amino terminal portion of IL-2” without providing the amino acid sequence.

Claim 3 has been amended to define X as (a) amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, and amino acids 21-24 of SEQ ID NO:30; (b) consecutive amino acids of such amino acids wherein the resulting X-Y polypeptide has apyrase activity; (c) a variant polypeptide 95% identical in sequence to such amino acids wherein the resulting X-Y polypeptide has apyrase activity, and (d) such amino acids with at least one conservative amino acid substitution wherein the resulting X-Y polypeptide has apyrase activity. As discussed above with respect to Claim 1, each of these sequences is within the scope of the elected embodiments. Support for this amendment can be found in the sequence listing as filed, and on page 9, line 35 to page 10, line 4; page 10, lines 10-37; page 38, lines 1-5; and page 39, lines 9-12. With respect to subpart (b), (c), and (d) of claim 3 and as discussed above, applicants have adequately described the polypeptides within the scope of these subparts by providing the amino acid

sequence in the sequence listing as filed. One of skill in the art would be able to select consecutive amino acids from such sequences or 95% identical to such sequences that when fused to soluble CD39 would retain apyrase activity. Moreover, using the guidance provided in the specification and the knowledge in the art at the time of filing, one of skill in the art would be able to identify conservative amino acid substitutions that would not destroy the apyrase activity of the fused polypeptide.

With respect to the enablement requirement and as discussed above, MPEP §2164.01 provides that the test for enablement requires a determination as to whether one of skill in the art can practice the claimed invention without *undue* experimentation. The claimed invention is a method for inhibiting platelet activation and recruitment in a mammal in need of such treatment comprising administering an effective amount of a soluble CD39 polypeptide consisting of a structure X-Y. As amended, Claim 3 provides sufficient direction as to the amino acid sequences for both the X and Y portion of the polypeptide. As discussed above, one skilled in the art, seeking to practice such a method can simply use the assays described in the specification to screen the polypeptides within the scope of subparts (b), (c), and (d) for apyrase activity and inhibition of platelet activity and recruitment. Accordingly, as amended, Claim 3 is both described and enabled by the specification.

Rejection of Claim 4 under §112, ¶1 – The Examiner asserts that the specification does not provide sufficient guidance as to the structure of a fusion polypeptide having the structure A-B-Y.

Applicants have canceled claim 4; therefore, this rejection is now moot.

Rejection of Claims 5-6 under §112, ¶1 – The Examiner asserts that the specification does not teach or describe fusion polypeptides comprising multiple polypeptides of SEQ ID NO: 6 as set forth in claim 5(b).

Applicants have canceled claim 6 and amended claim 5 to recite a method of inhibiting platelet activation and recruitment in a mammal in need of such treatment comprising administering an effective amount of a soluble CD39 polypeptide selected from the group consisting of: SEQ ID NO: 6, amino acids 25-464 of SEQ ID NO:27, amino acids 25-474 of SEQ ID NO:28, and amino acids 27-473 of SEQ ID NO:29, and amino acids 21-463 of SEQ ID NO:30. Each of these sequences is within the scope of the elected group because the sequences consist of an Ala residue or a portion of "IL-2 capable of adopting a stable secondary structure" fused to soluble CD39 as per elected Group I. The recitation to amino acids 21-476 of SEQ ID NO:3 and amino acids 21-476 of SEQ ID NO:4, which are directed to CD39-L4-soluble CD39 constructs, has been deleted as being drawn to non-elected embodiments. Applicants have deleted subpart (b) of claim 5, and therefore, the Examiner's rejection is now moot.

Rejection of Claims 20-35 under §112, ¶1 – The Examiner asserts that recombinant cells do not "encode" soluble CD39. The Examiner further argues that since the structure of the fusion soluble CD39 polypeptides are not adequately described, the claimed method for inhibiting platelet activity by using the undisclosed polypeptides made by the process of culturing recombinant host cells or the claimed method of administering such polypeptides alone or in combination with other antithrombotic or antiplatelet compositions is not adequately described.

Applicants have amended the term "encodes" to "expresses" in claims 20 and 21 as recombinant cells can express polypeptides. In light of the amendments to claims 1 and 5 discussed above, the polypeptides useful in the claimed method have been adequately described. Therefore, the method for using such polypeptides made by culturing recombinant cells and for administering such polypeptide alone or in combination with other antithrombotic or antiplatelet compositions is adequately described. Accordingly, this rejection should be withdrawn.

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Rejection of Claims 36-41 under §112, ¶1 – The Examiner argues that the specification does not adequately teach or describe which polypeptides having the structure X-Y or A-B-Y have apyrase activity, and therefore, there can be no support for using such polypeptides in treating disease.

Given the amendments to claims 1-3 and 5 (as discussed above), the specification adequately teaches and describes which claimed polypeptides can be used to inhibit platelet activation and recruitment in a mammal in need of such treatment . Moreover, the specification also discloses examples of using soluble CD39 to treat conditions involving thrombosis. For example, Example 19 shows that soluble CD39 inhibits microvascular thrombosis and confers cerebroprotection in a murine ischemic stroke model. Given this information, the specification adequately teaches and describes a method of preventing thrombus formation. One of ordinary skill in the art would recognize that such a method could be used to treat the diseases of Claims 36-37 that involve thrombosis formation or the risk of thrombosis formation. Similarly, one of ordinary skill in the art would recognize that such a method could be used in conjunction with the medical procedures of Claims 40-41 that involve thrombosis formation or the risk of thrombosis formation. Accordingly, this rejection should be withdrawn.

B. Section 112, Paragraph 2 Rejections of Claims 1 and 3

Claims 1 and 3 were rejected by the Examiner under 35 U.S.C. § 112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention.

Rejection of Claim 1 under §112, ¶2 – The Examiner argues that the phrase “polypeptide having an amino acid sequence as set forth in (SEQ ID NO:2) wherein the amino terminus is selected from the group consisting of amino acids 36-44 and the carboxyl terminus is selected from the group consisting of amino acids 471-478” is ambiguous because SEQ ID NO:2 already contains the amino terminus consisting of amino acids 36-44 and the carboxyl terminus consisting of amino acids 471-478.

Applicants have amended claim 1 to remove the contested language. Accordingly, this rejection should be withdrawn.

Rejection of Claim 3 under §112, ¶2 – The Examiner asserts that the phrase “amino terminal portion of mature IL-2” is ambiguous and indefinite because the term “portion” could be as little as one amino acid or it could be as long as 50 amino acids.

Applicants have amended claim 3 to remove the contested language. Accordingly, this rejection should be withdrawn.

C. The Art Rejections

The Examiner has rejected the pending claims under 35 U.S.C. § 103(a) as being unpatentable over WO 96/30532 in view of Maliszewski et al., Cullen et al., U.S. Patent No. 5,741,771, Gayle et al., or a combination thereof. Gayle et al. is the work of the inventors, and a declaration has been submitted with this reply by inventor Dr. Aaron J. Marcus, M.D. to remove Gayle et al. as a reference. Because none of the remaining references alone or in combination teach or suggest all the elements of the amended claims, the claims are non-obvious and should be allowed.

Section 103(a) Rejection of Claims 1-2, 20, 26, 32, 34, 36, 38 and 40

Claims 1-2, 20, 26, 32, 34, 36, 38 and 40 were rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over WO 96/30532 in view of Maliszewski et al. (J. Immunology 153:3574-83 (1994)).

WO 96/3052

WO 96/30532 is directed to a method for inhibiting platelet aggregation by administering a recombinant polypeptide having ATP diphosphohydrolase activity including soluble human CD39. WO 96/30532 does not teach using soluble CD39 that has the structure X-Y where X is Alanine, amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of

SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, or amino acids 21-24 of SEQ ID NO:30, and Y is soluble CD39, nor does it disclose the fusion polypeptide IL2-solCD39. In fact, WO 96/30532 does not disclose any structure for the soluble CD39 used in the method disclosed in the reference. The examples only disclose the use of whole cell lysates or membrane preparations of CD39 expressing COS-7 cells, and thus only disclose the use of membrane-bound CD39. See page 35. As such, the use of soluble CD39 in the method disclosed in WO 96/30532 is not adequately described or enabled.

Maliszewski et al.

Maliszewski et al. is directed to the cloning and molecular characterization of human and murine CD39. Maliszewski et al. describes the removal of the C-terminal hydrophobic region and its replacement with human Fc to demonstrate that the sequences proximal to this region are outside the cell. See p. 3581. As such, Maliszewski et al. does not disclose creating a fusion polypeptide with the structure X-Y where X is Alanine, amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, or amino acids 21-24 of SEQ ID NO:30, and Y is soluble CD39, nor does it disclose the fusion polypeptide IL2-solCD39. First, Maliszewski et al. does not teach using *soluble* CD39 but rather discloses the use of membrane bound CD39 as the transmembrane N-terminal portion is not removed. See p. 3581. Second, the fusion polypeptide disclosed in Maliszewski et al. is of the structure CD39-X rather than the structure claimed by the Applicants, X-solCD39.

Prima facie case of obviousness has not been established

Applicants respectfully traverse this rejection as the Examiner has not established a prima facie case of obviousness. "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

a. References do not teach or suggest all the claim limitations

Here, the prior art references when combined do not teach or suggest all the claim limitations of the amended Claim 1. Neither WO 96/30532 nor Maliszewski et al. are directed to a method for inhibiting platelet activation and recruitment comprising administering an effective amount of a soluble CD39 polypeptide consisting of a structure X-Y wherein X is an Ala residue, amino acids 1-15 of SEQ ID NO:6, amino acids 25-35 of SEQ ID NO:28, amino acids 27-34 of SEQ ID NO:29, or amino acids 21-24 of SEQ ID NO:30, and Y is soluble CD39. In fact, WO 96/30532 does not disclose any fusion polypeptides containing soluble CD39 much less a fusion protein having the specific claimed X-Y structure. Contrary to the Examiner's assertions, Maliszewski et al. does not disclose a fusion polypeptide of the structure X-Y where Y is soluble CD39. Rather, Maliszewski et al. discloses a membrane bound soluble CD39 as the transmembrane N-terminal portion is not removed. Moreover, Maliszewski et al. discloses that C-terminal hydrophobic region of this membrane bound soluble CD39 is replaced with human Fc. Thus, Maliszewski et al. describes a fusion polypeptide having the structure CD39-X where X is a human Fc region. Accordingly, the combination of references does not teach or suggest a method for inhibiting platelet activation and recruitment by administering a fusion polypeptide having the structure recited in Claim 1.

b. References do not provide a suggestion or motivation to combine

Moreover, the Examiner has not provided any suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to *combine* the teachings of WO 96/30532 and Maliszewski et al. This is not surprising as one of ordinary skill in the art would not be motivated to combine a reference involving soluble CD39 (WO 96/30532) with a reference involving membrane bound CD39 (Maliszewski et al.).

Accordingly, applicants respectfully request that this rejection be withdrawn.

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Section 103(a) Rejection of Claims 3-5, 21-25, 27, 29, 31, 33, 35, 37, 39 and 41

Claims 3-5, 21-25, 27, 29, 31, 33, 35, 37, 39 and 41 were rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over WO 96/30532 in view of Maliszewski et al. as applied to Claims 1-2, 20, 26, 32, 34, 36, 38 and 40 and further in view of Cullen et al. (DNA 7(9):645-50 (1988)).

The teachings of WO 96/30532 and Maliszewski et al. are discussed above.

Cullen et al.

Cullen et al. is directed to replacement of a natural interleukin-2 (IL-2) mRNA 5' non-coding region with a leader element derived from an efficiently translated rat preproinsulin II mRNA to enhance the expression of human IL-2. Cullen et al. describes modifications to the 5'-non-coding region and to the N-terminal portion of a signal peptide (which is removed upon secretion from the cell). There is no disclosure in Cullen et al. of CD39 nor is there any mention of methods of treatment utilizing soluble CD39 fusion polypeptides. Cullen et al. simply demonstrates that a certain leader sequence may be used to enhance expression of IL-2.

Cullen et al. has been mischaracterized

Contrary to the Examiner's assertions, Cullen et al. does not teach using an IL2 leader sequence with a heterologous polypeptide to increase secretion of the polypeptide. In fact, Cullen et al. discloses the *exact opposite*. Cullen et al. discloses replacing the leader sequence of natural IL2 with a preproinsulin II leader sequence. Thus, Cullen et al. cannot be combined with WO 96/30532 or Maliszewski to teach or suggest all the limitations of Claims 3 and 5 or their dependent claims. As discussed above, the combined teachings of WO 96/30532 and Maliszewski et al. do not teach or suggest a method using a polypeptide having the claimed structure X-Y. Cullen et al. does not cure this defect as it does not teach a method of using soluble CD39, much less one that has the claimed X-Y structure. Accordingly, Applicants respectfully request that this rejection be withdrawn.

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Section 103(a) Rejection of Claims 1, 28, and 30

Claims 1, 28, and 30 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over WO 96/30532 in view of U.S. Patent No. 5,741,771 ('771 patent).

The teaching of WO 96/30532 is discussed above.

The '771 patent

The '771 patent is directed to a method of treating a patient in need of thrombolytic or antithrombolytic therapy by administering simultaneously or sequentially a plasminogen activator and a thrombin activatable plasminogen analogue including the use of aspirin.

The '771 patent does not cure deficiencies discussed above

There is no disclosure in the '771 patent of CD39 nor is there any mention of methods of treatment utilizing soluble CD39 fusion polypeptides, or such fusion polypeptides in combination with antithrombotic or antiplatelet composition, or aspirin. Because the '771 patent does not cure the deficiencies of the teachings of WO 96/30532 as discussed above, the combination of the WO 96/30532 and the '771 patent do not teach or suggest all the limitations of Claim 1 and its dependent Claims 28 and 30. Accordingly, this rejection must be withdrawn.

Section 103(a) Rejection of Claims 1, 3-6, 21-25, 27, 29, 33, 35, 37, 39 and 41

Claims 1, 3-6, 21-25, 27, 29, 33, 35, 37, 39 and 41 were rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over WO 96/30532 in view of Gayle et al. (J. Clinical Investigation 101(9):1851-59 (May 1998)) as evidenced by Maliszewski et al.

The teachings of WO 96/30532 and Maliszewski et al. are discussed above.

Gayle et al. is not a proper reference

"Unless it is a statutory bar, a rejection based on a publication may be overcome by a showing that it was published by applicant himself/herself or on his/her behalf." MPEP §

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715.01(c). Here, Gayle et al. does not create a statutory bar as its publication date (May 1998) is less than one year before the priority date of the present application (October 1998). Accordingly, Gayle et al. may be removed as a reference.

Gayle et al. describes applicants own work. Section 715.01(c) of the MPEP provides that

[w]here the applicant is one of the co-authors of a publication cited against his or her application, . . . the applicant may overcome the rejection by filing a specific affidavit or declaration under 37 CFR 1.132 establishing that the article is describing applicant's own work. An affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction is sufficient to remove the publication as a reference under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982).

Applicants have submitted a declaration by Aaron J. Marcus ("Marcus Declaration"), one of the inventors of the application. The Marcus Declaration provides that the Gayle et al. reference describes the inventors own work and that the other co-authors of the Gayle et al. reference were working under one or more of the inventors' direction. The Marcus Declaration is sufficient to remove Gayle et al. as a reference. MPEP § 715.01(c); *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Accordingly, this rejection should be withdrawn.

Section 103(a) Rejection of Claims 29 and 31

Claims 29 and 31 were rejected by the Examiner under 35 U.S.C. § 103(a) over WO 96/30532 in view of Gayle et al. as evidenced by Maliszewski et al. as applied to Claims 1, 3-6, 21-25, 27, 29, 33, 35, 37, 39 and 41 and further in view of U.S. Patent No. 5,741,771.

Because the Gayle et al. reference has been removed as discussed above, this rejection should be withdrawn.

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D. Objections

Objection to Claims 3, 5, and 6 - The Examiner has objected to Claims 3, 5 and 6 as encompassing non-elected embodiments. Applicants have cancelled Claim 6 and amended Claims 3 and 5 to remove recitations to non-elected embodiments.

Objection to Claims 20-21 - The Examiner has objected to Claims 20-21 because the claims should state "The method" rather than "A method." Applicants have amended these claims to correct this language.

Objection to Claims 1 and 2 - The Examiner has objected to the use of the plural "polypeptides" in Claims 1 and 2 because it is inconsistent with the rest of the claim language. Claims 1 and 2 have been amended to eliminate the objectionable language.

Objection to Claim 5 - The Examiner has objected to the use of the plural "fusion polypeptides" in Claim 5(b) because it is inconsistent with the rest of the claim language. Claim 5 has been amended to eliminate the objectionable language.

Objection to Figure 4 - The Examiner has objected to Figure 4 as being too dark. Applicants enclose with this Reply another copy of Figure 4.

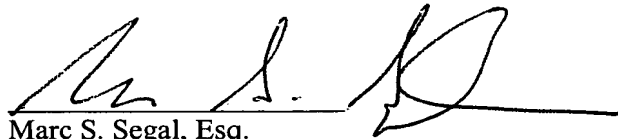
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Conclusion

In view of the proposed claim amendments and the arguments presented above, the present application is believed to be in condition for allowance and an early notice thereof is earnestly solicited. The Office is invited to contact the undersigned counsel in order to further the prosecution of this application in any way.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'M. S. Segal', is written over a horizontal line.

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